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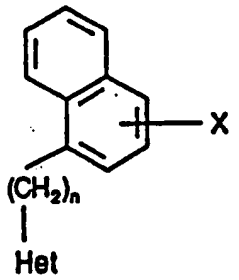
(54) Title: CHEMICAL COMPOUNDS

(57) Abstract

Angiotensin II receptor antagonists having formula (I) which are useful in the treatment of hypertension, congestive heart failure, renal failure, and glaucoma, pharmaceutical compositions including these antagonists, and methods of using these compounds to produce angiotensin II receptor antagonism in mammals.



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CHEMICAL COMPOUNDS

The present invention relates to new chemical compounds which are angiotensin II receptor antagonists and are useful in regulating hypertension induced or exacerbated by angiotensin II, and in the treatment of congestive heart failure, renal failure, and glaucoma. This invention also relates to pharmaceutical compositions containing these compounds and methods for using these compounds as antagonists of angiotensin II, as antihypertensive agents and as agents for treating congestive heart failure, renal failure, and glaucoma.

BACKGROUND OF THE INVENTION

The class of peptide pressor hormone known as angiotensin is responsible for a vasopressor action that is implicated in the etiology of hypertension in man. Inappropriate activity of the renin-angiotensin systems appears to be a key element in essential hypertension, congestive heart failure and in some forms of renal disease. In addition to a direct action on arteries and arterioles, angiotensin II (AII), being one of the most potent endogenous vasoconstrictors known, exerts stimulation on the release of aldosterone from the adrenal cortex. Therefore, the renin-angiotensin system, by virtue of its participation in the control of renal sodium handling, plays an important role in cardiovascular hemeostasis.

Interruption of the renin-angiotensin system with converting enzyme inhibitors, such as captopril, has proved to be clinically useful in the treatment of hypertension and congestive heart failure (Abrams, W.B., et al., (1984), Federation Proc., 43, 1314). The most direct approach towards inhibition of the renin-angiotensin system would block the action of AII at the receptor. Compelling evidence suggests that AII also contributes to renal vasoconstriction and sodium

retention that is characteristic of a number of disorders such as heart failure, cirrhosis and complications of pregnancy (Hollenberg, N.K., (1984), J. Cardiovas. Pharmacol., 6, S176). In addition, recent animal studies suggest that inhibition of the renin-angiotensin system may be beneficial in halting or slowing the progression of chronic renal failure (Anderson, S., et al., (1985), J. Clin. Invest., 76, 612). Also, a recent patent application (South African Patent Application No. 87/01,653) claims that AII antagonists are useful as agents for reducing and controlling elevated intraocular pressure, especially glaucoma, in mammals.

The compounds of this invention inhibit, block and antagonize the action of the hormone AII, and are therefore useful in regulating and moderating angiotensin induced hypertension, congestive heart failure, renal failure and other disorders attributed to the actions of AII. When compounds of this invention are administered to mammals, the elevated blood pressure due to AII is reduced and other manifestations based on AII intercession are minimized and controlled. Compounds of this invention are also expected to exhibit diuretic activity.

Recognition of the importance of blocking and inhibiting the actions of AII has stimulated other efforts to synthesize antagonists of AII. The following references have disclosed imidazole derivatives which are described as having AII blocking activity and useful as hypotensive agents.

Furukawa et al., U.S. Patent 4,340,598 discloses imidazol-5-yl-acetic acids and imidazol-5-yl-propanoic acids. Specifically, the discloser includes 1-benzyl-2-n-butyl-5-chloroimidazole-4-acetic acid and 1-benzyl-2-phenyl-5-chloroimidazole-4-propanoic acid.

Furukawa, et al., U.S. Patent 4,355,040 discloses substituted imidazole-5-acetic acid derivatives. A

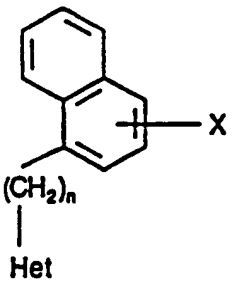
compound specifically disclosed is 1-(2-chlorobenzyl)-2-n-butyl-4-chloroimidazole-5-acetic acid.

Carini et al. in EP 253,310 disclose certain imidazolylpropenoic acids. Two intermediates described in this patent are ethyl 3-[1-(4-nitrobenzyl)-2-butyl-4-chloroimidazol-5-yl]propenoate and ethyl 3-[2-butyl-4-chloro-1-(4-aminobenzyl)imidazol-5-yl]propenoate.

Also, Wareing, in PCT/EP 86/00297, discloses as intermediates certain imidazolylpropenoate compounds. On page 62, Formula (CX) is ethyl 3-[1(-4-fluorophenyl)-4-isopropyl-2-phenyl-1H-imidazol-5-yl]-2-propenoate.

DESCRIPTION OF THE INVENTION

The compounds of the present invention that are blockers of angiotensin II receptors are represented by the following Formula (I):



(I)

in which:

X is absent or present as any accessible combination of up to three substituents selected from Cl, Br, F, I, CF_3, C_{1-6}alkyl, NO_2, A-CO_2R^1, tetrazolyl, C_{1-6}alkoxy, OH, SC_1-$_6$alkyl, SO_2NHR^1, $NHSO_2R^7$, SO_3H, $CONR^1R^1$, CN, SO_2C_{1-6}alkyl, NR^1R^1, NR^1COH, or NR^1COC_{1-6}alkyl;

each R^1 independently is hydrogen, C_{1-6}alkyl, or $(CH_2)_n$phenyl, wherein the phenyl is unsubstituted or substituted by any accessible combination of up to three substituents selected from Cl, Br, F, I, CF_3, or C_{1-6}alkyl;

A is $-(CH_2)_n-$, $-CH=CH-$, $-Q-CH(R^6)-$, or $-Q-(CH_2)_m-U-(CH_2)_m-$;

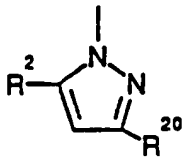
each n independently is 0-4;

each m independently is 1-2;

Q is O, S, NH, NC_{1-6}alkyl;

U is absent or present as O, S, NH, or NC_{1-6}alkyl;

Het is



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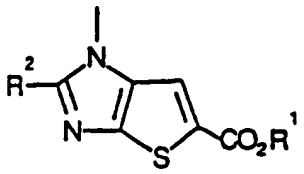

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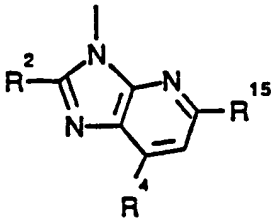

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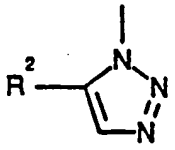

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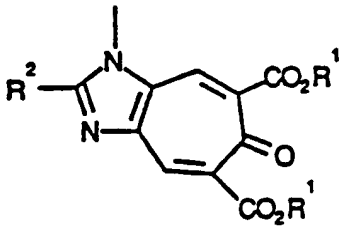

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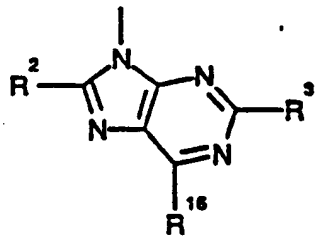

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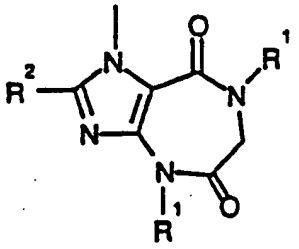

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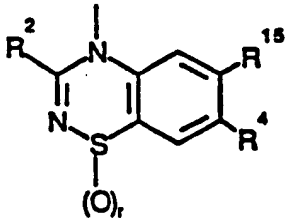

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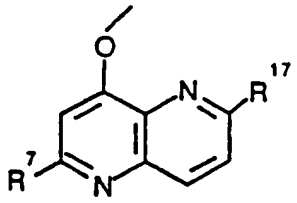

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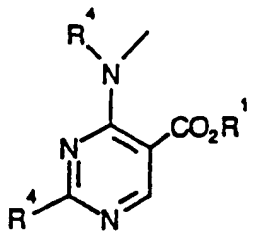

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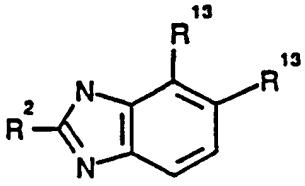

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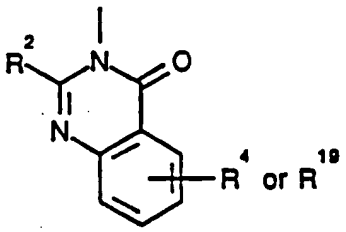

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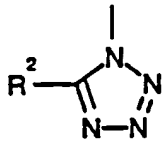

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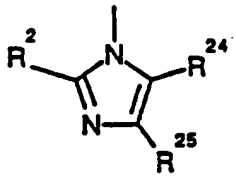

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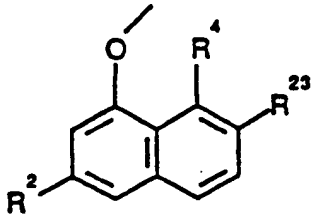

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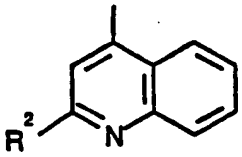

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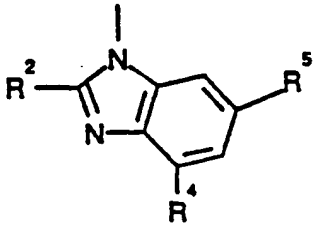

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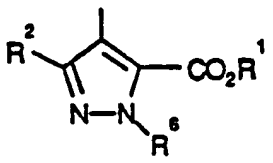

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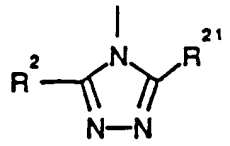

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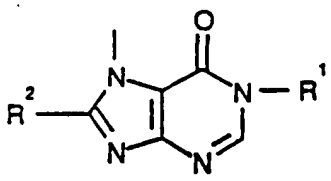

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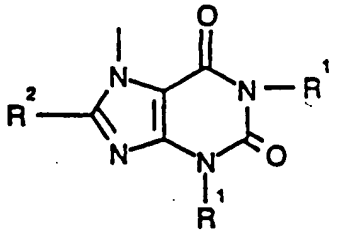

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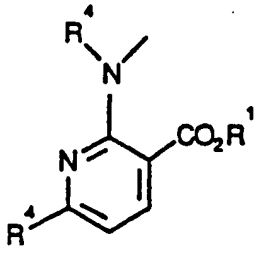

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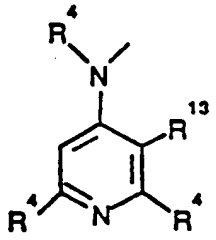

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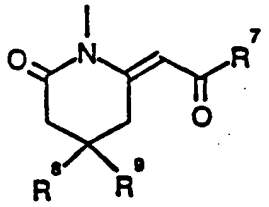

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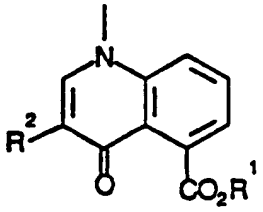

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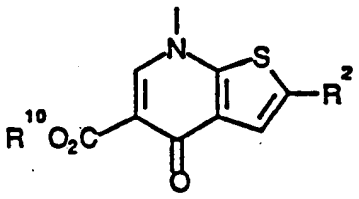

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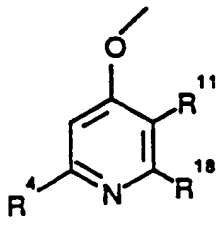

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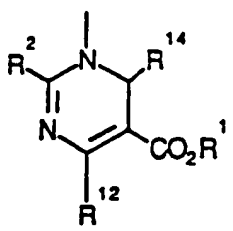

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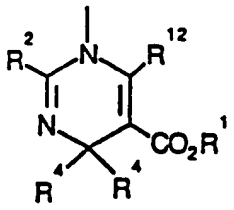

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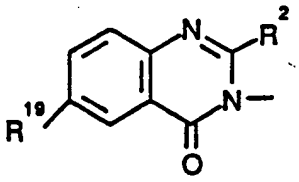

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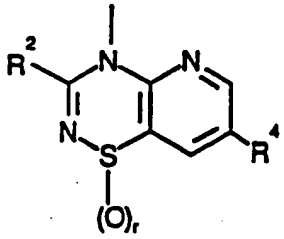

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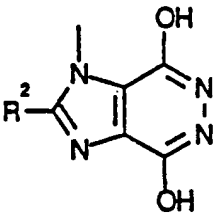

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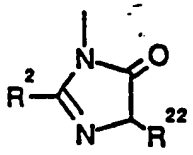

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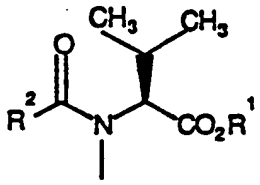
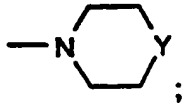


(34) ;

each R^2 independently is C_{1-8}alkyl, $-OC_{2-8}$alkyl, $-SC_{2-8}$alkyl, $-(CH_2)_{0-2}C_{3-6}$cycloalkyl, $-O(CH_2)_{0-2}$phenyl, or $-S(CH_2)_{0-2}$phenyl, wherein the phenyl is unsubstituted or substituted by any accessible combination of up to three substituents selected from Cl, Br, F, I, CF_3, or C_{1-6}alkyl;

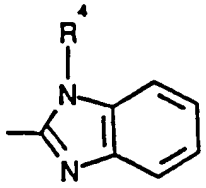
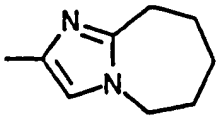
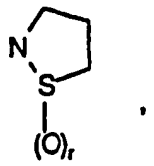
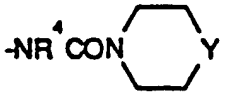
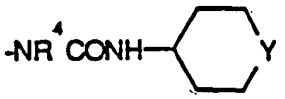
R^3 is Cl, Br, F, I, CF_3, SC_{1-6}alkyl, NR^4R^4, or



;

each R^4 independently is H or C_{1-6}alkyl;

R^5 is

or $-NR^4CONR^4R^4$;

each R^6 independently is H, C_{1-6}alkyl, $-(CH_2)_{1-2}CF^3$, $-(CH_2)_{1-2}C_{3-6}$cycloalkyl, or $-(CH_2)_{0-2}$phenyl, wherein the phenyl is unsubstituted or substituted by any accessible combination of up to three substituents selected from Cl, Br, F, I, CF_3, or C_{1-6}alkyl;

each R^7 independently is C_{1-4}alkyl or C_{1-4}alkoxy;

R^8 and R^9 independently is C_{1-4}alkyl or R^8 and R^9 taken together are $-(CH_2)_{4-6}-$;

R^{10} is H, C_{1-4}alkyl, or $-(CH_2)_{1-2}OCH_3$;

R^{11} is H, C_{1-4}alkyl, $-(CH_2)_{1-4}-OH$, or CO_2R^1 and R^{18} is R^4 or R^{11} and R^{18} taken together are $-(CH_2)_3-$ or $-(CH_2)_4-$;

each R^{12} independently is H, C_{1-4}alkyl, Cl, Br, F, or I;

each R^{13} independently is CO_2R^1, Cl, Br, F, or I;

R^{14} is C_{1-4}alkyl or =0;

each R^{15} independently is H, C_{1-4}alkyl, or CO_2R^1;

R^{16} is H, C_{1-4}alkyl, Cl, Br, F, I, SC_{1-4}alkyl, or NR^4R^4;

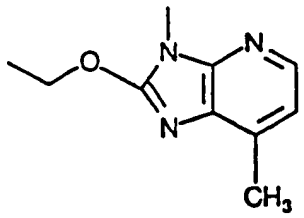
R^{17} is H, C_{1-4}alkoxy, or NR^4R^4;

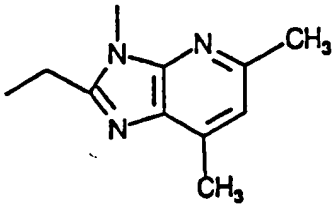
R^{19} is H, NR^4R^4, or $NR^4C(O)NR^4R^4$;

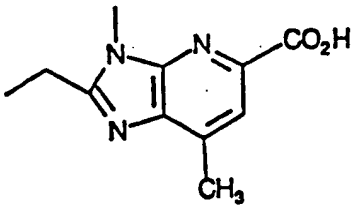
R^{20} is $-(CH_2)_{1-3}-O-CH_3$, $-(CH_2)_{0-3}-CO_2R^4$ or R_2;

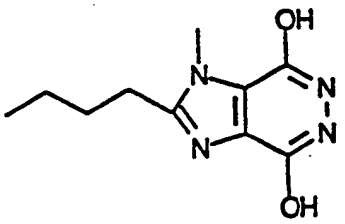
R^{21} is C_{1-6}alkyl, $-(CH_2)_{1-4}OH$, $-(CH_2)_{1-3}-O-CH_3$, $-(CH_2)_{1-2}$-phenyl or $-SCH_2$-phenyl, wherein the phenyl is unsubstituted or substituted by CO_2R^1, Cl, Br, F, or I;

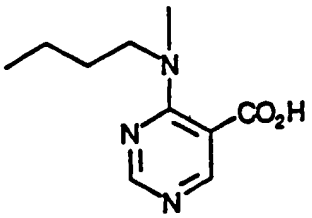
R^{22} is $-(CH_2)_3-$ or $-(CH_2)_4-$;

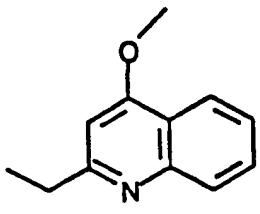


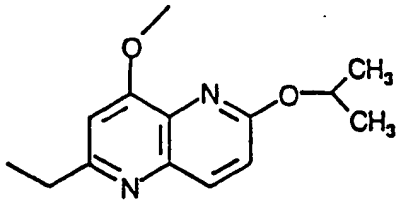


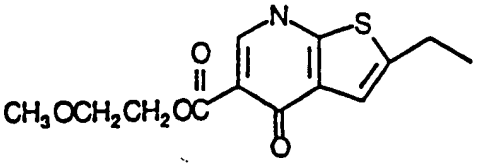


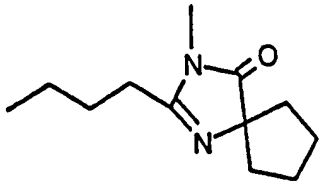




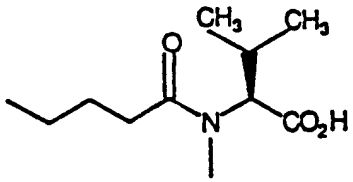








and



The invention also relates to pharmaceutical compositions comprising a pharmaceutical carrier and an effective amount of a compound of Formula (I).

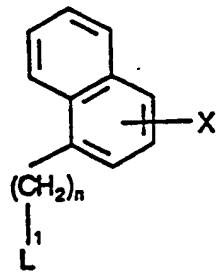
Also included in the present invention are methods for antagonizing angiotensin II receptors which comprises administering to a subject in need thereof an effective amount of a compound of Formula (I). Methods of treating hypertension, congestive heart failure, glaucoma, and renal failure by administering these compounds are also included in this invention.

Because the compounds of Formula (I) are angiotension II receptor antagonists, they may also be of value in the treatment of left ventricular hypertrophy regression, diabetic nephropathy, diabetic retinopathy, macular degeneration, haemorrhagic stroke, angina, and anxiety. Additionally, these compounds may

be expected to be useful in the primary and secondary prevention of infarction, in the prevention of atheroma progression and in the regression of antheroma, in the prevention of restinosis after angioplasty or bypass surgery and in the improvement of cognitive funtion.

The compounds of this invention are prepared by procedures described herein and illustrated by the examples. Reagents, protecting groups and functionality on the naphthalene and other fragments of the molecule must be consistent with the proposed chemical transformations. Steps in the synthesis must be compatible with the functional groups and the protecting groups on the naphthalene and other parts of the molecule.

The compounds of Formula (I) are generally prepared by reacting a compound of the formula (II) with a compound of the formula (III):



Het-L^2

(II) (III)

wherein X, n and Het are as defined in Formula (I), with any reactive functional groups protected;

L^1 is a displaceable group; and

L^2 is an alkali metal salt;

and thereafter removing any protecting groups, and optionally forming a pharmaceutically acceptable salt.

As used hereinabove, the term "displaceable group" means a halide, mesylate, tosylate, or acetate group and the term "alkali metal salt" means a sodium, lithium, or potassium salt. By the term "reactive functional groups protected" is meant that certain groups on the naphthyl

or Het rings are protected, for example a CO_2H group is protected as its C_{1-4}alkyl ester derivative and a hydroxy group is protected as its C_{1-4}alkoxy or benzyloxy derivative.

The substituted naphthyl-$(CH_2)_n$ -group is incorporated onto the Het ring by known procedures, for example, by reaction with a substituted naphthyl-$(CH_2)_n$ halide, mesylate, tosylate, or acetate, such as methyl 4-bromomethylnaphthalene-1-carboxylate, in a suitable solvent, such as dimethylformamide (DMF), in the presence of a suitable base, such as an alkali metal hydride, or potassium or sodium carbonate, preferably potassium carbonate, at a reaction temperature of about 25°C to about 100°C, preferably at about 70°C.

The substituted naphthyl-$(CH_2)_n$ halides, mesylates of acetates of Formula (II) are known to the art or are synthesized by known procedures [Can. J. Chem., 59:2629 (1981)]. For example, methyl 4-methylnaphthalene-1-carboxylate is methyl halogenated using, for example, N-bromosuccinimide in the presence of an initiator, such as benzoylperoxide, and UV light, in a suitable solvent, such as carbon tetrachloride.

The various Het compounds used in the synthesis Fomula (I) compounds are prepared employing conventional techniques. Each of Het compounds is treated with a base, such as an alkali metal hydride, for example sodium, lithium or potassium hydride, or sodium or potassium carbonate, to prepare the formula (III) compounds. The publications hereinbelow detail the preparation of the various Het compounds and reference should be made to such publications for their disclosure, which are incorporated herein by reference.

Methods for preparing Het compounds herein Het is a pyrazole of formula (1) and (18) are detailed in U.S. Patent No. 5,081,127, EP Publication Nos. 323 841, 411 507, 446 062, and 449 699 and PCT Publication No. WO 91/15479.

Methods for preparing Het compounds wherein Het is a imidazothiophene of formula (2) are detailed in EP Publication No 407 102.

Methods for preparing Het compounds wherein Het is a imidazopyridine of formula (3) are detailed in EP Publication Nos. 399 731, 400 974, 420 237, and 456 510 and U.S. Patent Nos. 5,053,329 and 5,102,880.

Methods for preparing Het compounds wherein Het is a triazole of formula (4) and (19) are detailed in EP Publication Nos. 323 841, 409 332, and 412 594 and U.S. Patent No. 5,093,346.

Methods for preparing Het compounds wherein Het is a imidazole fused to a 7 membered carbocyclic ring of formula (5) are detailed in EP Publication No. 432 737.

Methods for preparing Het compounds wherein Het is a imidazopyrimidine of formula (6) are detailed in EP Publication No. 399 731.

Methods for preparing Het compounds wherein Het is a benzodiazepine of formula (7) are detailed in U.S. Patent No. 5,064,825.

Methods for preparing Het compounds wherein Het is a benzothiadiazine of formula (8) are detailed in Weller, et al., Bioorganic & Medicinal Chemistry Letters, 2(9):1115 (1992).

Methods for preparing Het compounds wherein Het is a pyridopyridine of formula (9) are detailed in EP Publication No. 487 252 and PCT Publication No. WO 91/07404.

Methods for preparing Het compounds wherein Het is a aminopyrimidine of formula (10) are detailed in EP Publication No. 475 206.

Methods for preparing Het compounds wherein Het is a benzimidazole of formula (11) and (17) are detailed in EP Publication Nos. 392 317, 468 470, 400 835, 425,921 and 459,136, U.S. Patent No. 4,880,804 and German Patent Nos. 4,031,287 and 3,928,177.

Methods for preparing Het compounds wherein Het is

a benzopyrimidine of formula (12) and (30) are detailed in EP Publication Nos. 411 766, 481 614, 407 342, and 445 811.

Methods for preparing Het compounds wherein Het is a tetrazole of formula (13) are detailed in EP Publication No. 323 841.

Methods for preparing Het compounds wherein Het is an imidazole of formula (14) are detailed in EP Publication Nos. 253 310, 324 377, 380 959, 409 332 and 479 479.

Methods for preparing Het compounds wherein Het is a quinoline of formula (15) and (16) are detailed in EP Publication Nos. 412 848 and 456 442 and Great Britain Patent No. 2,234,748.

Methods for preparing Het compounds wherein Het is a imidazopyrimidinone of formula (20) are detailed in EP Publication No. 467 207.

Methods for preparing Het compounds wherein Het is a imidazopyrimidine-dione of formula (21) are detailed in EP Publication No. 430 300.

Methods for preparing Het compounds wherein Het is a aminopyridine of formula (22) and (23) are detailed in EP Publication No. 475 206.

Methods for preparing Het compounds wherein Het is a piperidine of formula (24) are detailed in Murray, et al., Bioorganic & Medicinal Chemistry Letters, 2(12): 1775 (1992).

Methods for preparing Het compounds wherein Het is a quinolone of formula (25) are detailed in EP Publication No.498 721.

Methods for preparing Het compounds wherein Het is a pyridothiophene of formula (26) are detailed in EP Publication No. 443 568.

Methods for preparing Het compounds wherein Het is a alkoxypyridine of formula (27) are detailed in EP Publication Nos. 453 210 and PCT Publication No. WO 91/19697.

Methods for preparing Het compounds wherein Het is a dihydropyrimidine of formula (28) and (29) are detailed in EP Publication No. 481 448.

Methods for preparing Het compounds wherein Het is a pyridothiadiazine of formula (31) are detailed in Weller, et al., Bioorganic & Medicinal Chemistry Letters, 2(9):1115 (1992).

Methods for preparing Het compounds wherein Het is a imidazopyridazine of formula (32) are detailed in PCT Publication No. WO 91/19715.

Methods for preparing Het compounds wherein Het is a imidazolone of formula (33) are detailed in PCT Publication No. WO 91/14679.

Methods for preparing Het compounds wherein Het is an acylated alpha amino acid derivative of formula (34) are detailed in EP Publication No. 443 983.

Compounds of Formula (I) in which the naphthyl group is substituted by hydroxy are formed from Formula (I) compounds in which the naphthyl already present is substituted by C_1-C_4alkoxy using an ether-cleaving reagent, such as boron tribromide or hydrobromic acid.

Compounds of Formula (I) in which the naphthyl group is substituted by carboxy are formed from Formula (I) compounds in which the naphthyl group is substituted by CO_2C_{1-4}alkyl using basic hydrolysis, such as aqueous sodium or potassium hydroxide in methanol or ethanol, or using acidic hydrolysis, such as aqueous hydrochloric acid.

Compounds of Formula (I) in which the naphthyl group is substituted by a tetrazol-5-yl group are prepared from the correponding carboxy compounds. For example, Formula (I) acid compounds are reacted with a halogenating agent, such as thionyl chloride, in a suitable solvent, for example benzene, to give the corresponding acid halide compounds. The acid halides are then converted to primary amide compounds in a

reaction with concentrated ammonia to give Formula (I) compounds wherein the naphthyl group is substituted by $CONH_2$. Subsequent dehydration of the amides with oxalyl chloride/dimethylformamide in acetonitrile/dimethylformamide yields the nitrile compounds, which are the immediate precursors to the Formula (I) tetrazole compounds. Tetrazole formation is accomplished by reacting the nitriles with azide, preferably aluminum azide prepared in situ by the reaction of sodium azide with aluminum chloride, in a suitable solvent, for example tetrahydrofuran.

Pharmaceutically acceptable acid addition salts of compounds of Formula (I) are formed with appropriate organic or inorganic acids by methods known in the art. For example, the base is reacted with a suitable inorganic or organic acid in an aqueous miscible solvent such as ethanol with isolation of the salt by removing the solvent or in an aqueous immiscible solvent when the acid is soluble therein, such as ethyl ether or chloroform, with the desired salt separating directly or isolated by removing the solvent. Representative examples of suitable acids are maleic, fumaric, benzoic, ascorbic, pamoic, succinic, bismethylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, hydrochloric, hydrobromic, sulfuric, cyclohexylsulfamic, phosphoric and nitric acids.

Pharmaceutically acceptable base addition salts of compounds of Formula (I) are prepared by known methods from organic and inorganic bases, including nontoxic alkali metal and alkaline earth bases, for example, calcium, lithium, sodium, and potassium hydroxide; ammonium hydroxide, and nontoxic organic bases, such as triethylamine, butylamine, piperazine, meglumine, choline, diethanolamine, and tromethamine.

Angiotensin II antagonist activity of the compounds of Formula (I) is assessed by in vitro and in vivo methods. In vitro antagonist activity is determined by the ability of the compounds to compete with ^{125}I-angiotensin II for binding to vascular angiotensin II receptors and by their ability to antagonize the contractile response to angiotensin II in the isolated rabbit aorta. In vivo activity is evaluated by the efficacy of the compounds to inhibit the pressor response to exogenous angiotensin II in conscious rats and to lower blood pressure in a rat model of renin dependent hypertension.

Binding

The radioligand binding assay is a modification of a method previously described in detail (Gunther et al., Circ. Res. 47:278, 1980). A particular fraction from rat mesenteric arteries is incubated in Tris buffer with 80 pM of ^{125}I-angiotensin II with or without angiotensin II antagonists for 1 hour at 25°C. The incubation is terminated by rapid filtration and receptor bound ^{125}I-angiotensin II trapped on the filter is quantitated with a gamma counter. The potency of angiotensin II antagonists is expressed as the IC_{50} which is the concentration of antagonist needed to displace 50% of the total specifically bound angiotensin II.

Aorta

The ability of the compounds to antagonize angiotensin II induced vasoconstriction is examined in the rabbit aorta. Ring segments are cut from the rabbit thoracic aorta and suspended in organ baths containing physiological salt solution. The ring segments are mounted over metal supports and attached to force displacement transducers which are connected to a recorder. Cumulative concentration response curves to angiotensin II are performed in the absence of

antagonist or following a 30-minute incubation with antagonist. Antagonist disassociation constants (K_B) are calculated by the dose ratio method using the mean effective concentrations.

Inhibition of pressor response to angiotensin II in conscious rats

Rats are prepared with indwelling femoral arterial and venous catheters and a stomach tube (Gellai et al., Kidney Int. 15:419, 1979). Two to three days following surgery the rats are placed in a restrainer and blood pressure is continuously monitored from the arterial catheter with a pressure transducer and recorded on a polygraph. The change in mean arterial pressure in response to intravenous injections of 250 mg/kg angiotensin II is compared at various time points prior to and following the administration of the compounds intravenously or orally at doses of 0.1 to 300 mg/kg. The dose of compound needed to produce 50% inhibition of the control response to angiotensin II (IC_{50}) is used to estimate the potency of the compounds.

Antihypertensive activity

The antihypertensive activity of the compounds is measured by their ability to reduce mean arterial pressure in conscious rats made renin-dependent hypertensive by ligation of the left renal artery (Cangiano et al., J. Pharmacol. Exp. Ther. 208:310, 1979). Renal artery ligated rats are prepared with indwelling catheters as described above. Seven to eight days following renal artery ligation, the time at which plasma renin levels are highest, the conscious rats are placed in restrainers and mean arterial pressure is continuously recorded prior to and following the administration of the compounds intravenously or orally. The dose of compound needed to reduce mean arterial pressure by 30 mm Hg (IC_{30}) is used as an estimate of

potency.

The intraocular pressure lowering effects employed in this invention may be measured by the procedure described by Watkins, et al., J. Ocular Pharmacol., 1 (2):161-168 (1985).

The compounds of Formula (I) are incorporated into convenient dosage forms, such as injectable preparations, or for orally active compounds, capsules or tablets. Solid or liquid pharmaceutical carriers are employed. Solid carriers include starch, lactose, calcium sulfate dihydrate, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Liquid carriers include syrup, peanut oil, olive oil, saline, and water. Similarly, the carrier or diluent may include any prolonged release material, such as glyceryl monostearate or glyceryl distearate, alone or with a wax. The amount of solid carrier varies widely but, preferably, will be from about 25 mg to about 1 g per dosage unit. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion, soft gelatin capsule, sterile injectable liquid, such as an ampoule, or an aqueous or nonaqueous liquid suspension.

For topical ophthalmolgic administration, the pharmaceutical compositions adapted include solutions, suspensions, ointments, and solid inserts. Typical pharmaceutically acceptable carriers are, for example, water, mixtures of water and water-miscible solvents such as lower alkanols or vegetable oils, and water soluble ophthalmologically acceptable non-toxic polymers, for example, cellulose derivatives such as methyl cellulose. The pharmaceutical preparation may also contain non-toxic auxiliary substances such as emulsifying, preserving, wetting, and bodying agents, as for example, polyethylene glycols; antibacterial components, such as quarternary ammonium compounds; buffering ingredients, such as alkali metal chloride;

antioxidants, such as sodium metabisulfite; and other conventional ingredients, such as sorbitan monolaurate.

Additionally, suitable ophthalmic vehicles may be used as carrier media for the present purpose including conventional phosphate buffer vehicle systems.

The pharmaceutical preparation may also be in the form of a solid insert. For example, one may use a solid water soluble polymer as the carrier for the medicament. Solid water insoluble inserts, such as those prepared from ethylene vinyl acetate copolymer, may also be utilized.

The pharmaceutical preparations are made following conventional techniques of a pharmaceutical chemist involving mixing, granulating, and compressing, when necessary, for tablet forms, or mixing, filling and dissolving the ingredients, as appropriate, to give the desired oral, parenteral, or topical products.

Doses of the compounds of Formula (I) in a pharmaceutical dosage unit as described above will be an efficacious, nontoxic quantity selected from the range of .01 - 200 mg/kg of active compound, preferably 1 - 100 mg/kg. The selected dose is administered to a human patient in need of angiotensin II receptor antagonism from 1-6 times daily, orally, rectally, topically, by injection, or continuously by infusion. Oral dosage units for human administration preferably contain from 1 to 500 mg of active compound. Preferably, lower dosages are used for parenteral administration. Oral administration, at higher dosages, however, also can be used when safe and convenient for the patient. Topical formulations contain the active compound in an amount selected from 0.0001 to 0.1 (w/v%), preferably from 0.0001 to 0.01. As a topical dosage unit form, an amount of active compound from between 50 ng to 0.05 mg, preferably 50 ng to 5 mg, is applied to the human eye.

The compounds of this invention may be co-administered with other pharmaceutically active

compounds for example in combination, concurrently or sequentially. Conviently the compounds of this invention and the other active compound or compounds are formulated in a pharmaceutical composition. Examples of compounds which may be included in pharmaceutical compositions with the compounds of Formula (I) are diuretics, such as thiazides and related compounds, for example bendrofluazide, chlorthiazide, chlorthalidone, and hydrochlorothiazide, and other diuretics, for example frusemide and triamterene, calcium channel blockers, for example verapamil and nifedipine, ß-adrenoceptor blockers, for example propanolol, renin inhibitors, for example enalkinen and angiotensin converting enzyme inhibitors, for example captopril and enapril.

The method of this invention of antagonizing angiotensin II receptors in mammals, including humans, comprises administering to a subject in need of such antagonism an effective amount of a compound of Formula (I). The methods of this invention of treating hypertension, congestive heart failure, glaucoma, and renal failure comprise administering a compound of Formula (I) to a subject in need thereof an effective amount to produce said activity.

Contemplated equivalents of Formula (I) compounds are compounds otherwise corresponding thereto wherein substituents have been added to any of the unsubstituted positions of the Formula (I) compounds provided such compounds have the pharmaceutical utility of Formula (I) compounds.

The following examples illustrate preparation of compounds and pharmaceutical compositions of this invention. The examples are not intended to limit the scope of this invention as defined hereinabove and as claimed below.

Example 1

2-n-Butyl-1-[(4-carboxynaphth-1-yl)methyl]-6-[N-(cyclohexylaminocarbonyl)amino]benzimidazole

(i) 2-n-butyl-6-[N-(cyclohexylaminocarbonyl)-amino]-benzimidazole

The title compound is prepared according to the procedure of EP Publication No. 392 317.

(ii) 2-n-butyl-1-[(4-carbomethoxynaphth-1-yl)methyl]-6-[N-(cyclohexylaminocarbonyl)-amino]benzimidazole

A suspension of 0.214 mol of powdered potassium carbonate, 0.214 mol of 2-n-butyl-6-[N-(cyclohexyl-aminocarbonyl)amino]benzimidazole and 0.235 mol of methyl 4-bromomethylnaphthalene-1-carboxylate (E.A. Dixon, A. Fischer, and F.P. Robinson, Can. J. Chem. 59, 2629 (1981)) in 600 mL of dimethylformamide is stirred for 5 hours under argon at 70°C. An additional 0.0235 mol of the bromomethyl ester is added and the suspension is stirred an additional 15 hours at 70°C. The reaction mixture is poured into water and the resulting solid is collected by filtration, washed with water, and triturated several times with boiling methanol.

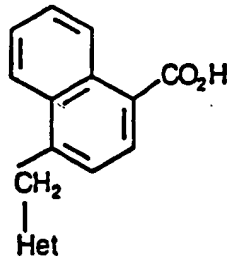
(iii) 2-n-butyl-1-[(4-carboxynaphth-1-yl)methyl]-6-[N-(cyclohexylaminocarbonyl)amino]-benzimidazole

A slurry containing 26.14 mmol of 2-n-butyl-1-[(4-carbomethoxynaphth-1-yl)methyl]-6-[N-(cyclohexyl-aminocarbonyl)amino]benzimidazole and 2.09 mmol of potassium hydroxide in a mixture of 165 mL of ethanol and 85 mL of water is stirred at ambient temperature for 18 hours. Concentration under vacuum and dilution with water gives a clear solution. Adjustment of the pH to about 4 with hydrochloric acid gives the title compound.

Examples 2-21

Examples 2-20 in Table I are prepared following the procedure of Example 1 using the appropriate Het group in place of 2-n-butyl-6-[N-(cyclohexylaminocarbonyl)-amino]benzimidazole.

Table I



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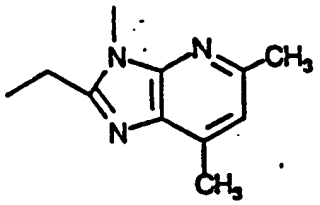
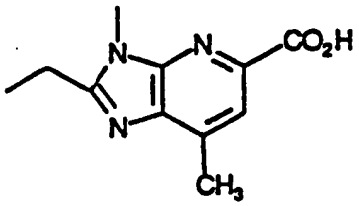
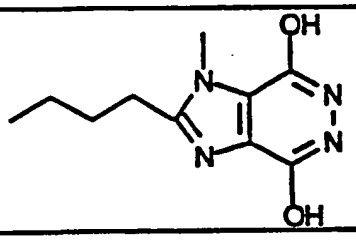
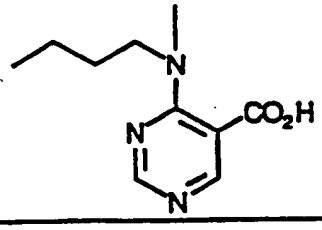
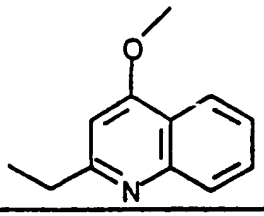
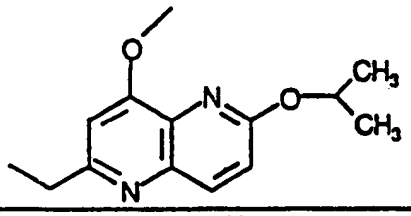
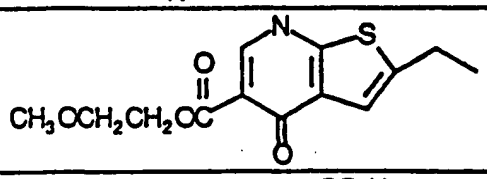
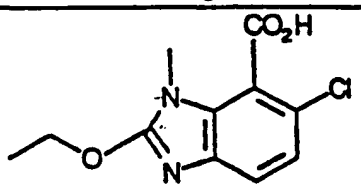
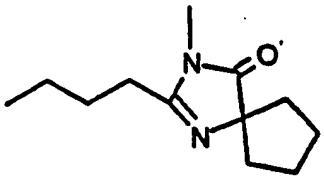
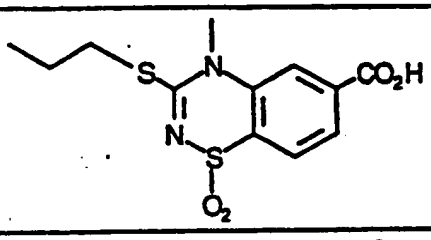
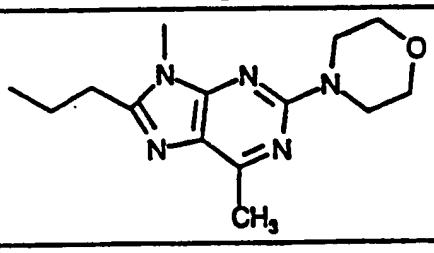
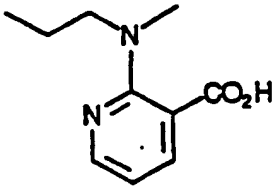
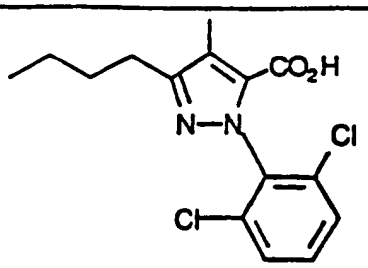
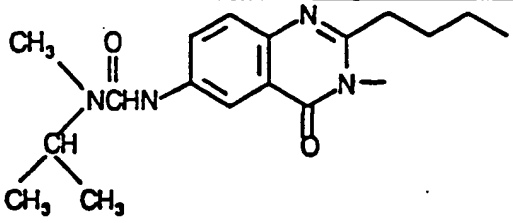
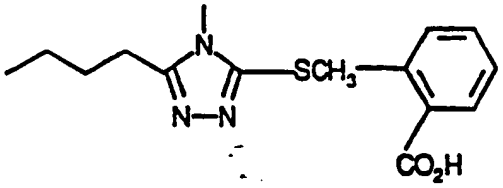
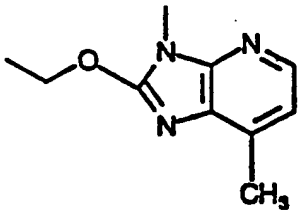
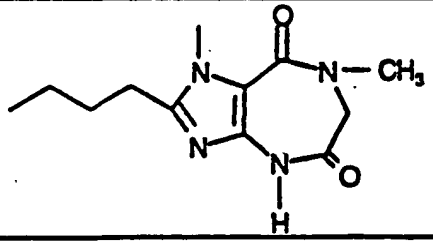
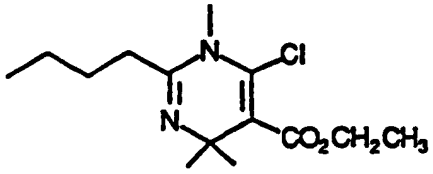
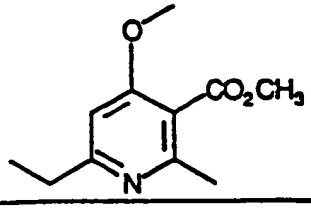
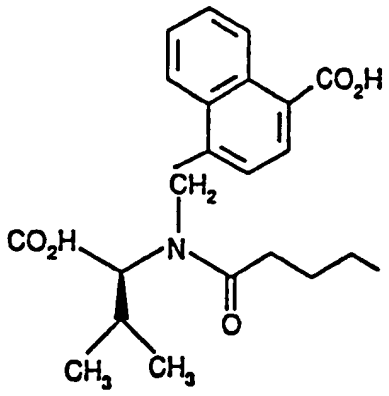
2	
3	
4	
5	

6	
7	
8	
9	
10	
11	
12	
13	

14	
15	
16	
17	
18	
19	
20	

Example 21



N-[(1-Carboxynaphth-4-yl)methyl]-N-valeryl-L-valine.

A solution of methyl 4-bromomethylnapthalene-1-carboxylate (2.0g, 7.16 mmol), L-valine methyl ester hydrochloride (1.44g, 8.59 mmol) and 5 mL of disopropylethylamine in 15 mL of dimethylformamide was heated to 75°C for 1 hour and then allowed to stand at ambient temperature for 5 days. The reaction mixture was then poured into water and extracted twice with ethyl acetate. The combined ethyl acetate extracts were washed with 5% sodium bicarbonate solution, dried over magnesium sulfate, and concentrated to give an oil (TLC R_f, SiO_2, 20% ethyl acetate/hexane). The unpurified product (2.3g, 7 mmol) was dissolved in 25 mL of methylene chloride and was treated with 2.7 g (21 mmol) of disopropylethylamine and 1.09 g (9.1 mmol) of valeryl chloride. The reaction mixture was stirred at ambient temperature for 8 hours and then an additional 1 g of valeryl chloride was added and the mixture was stirred for one hour. Then 25 mL of 5% sodium bicarbonate solution was added, the mixture was stirred for 1 hour and then extracted with methylene chloride. The extract was dried and chromatographed (on silica gel, eluting with 5% ethyl acetate/methylene chloride) to give 2.44 g of an oil (the amide diester). A solution of 1.5 g (3.63 mmol) of this product and 1.27 g

(22.6 mmol) of potassium hydroxide in a mixture of 60 mL of ethanol and 10 mL of water was stirred at ambient temperature for 5 days. The reaction mixture was concentrated under vacuum and 30 mL of water was added. Addition of 12 N hydrochloric acid solution to pH 2 gave 1.07 g of a white solid, mp 106-108°C. (The NMR was consistent for the di-acid, but the elemental analysis indicated the presence of potassium.) After stirring the product with aqueous hydrochloric acid at pH 1 for 1 hour, 1.0 g of white crystals were obtained, mp 112-114°C. Anal. Calcd for $C_{22}H_{27}NO_5 \cdot \frac{1}{2}H_2O$; C,66.99; H, 7.15; N, 3.55. Found: C, 66.90; H, 7.09; N, 3.95.

Example 22

An oral dosage form for administering orally active Formula (I) compounds is produced by screening, mixing and filling into hard gelatin capsules the ingredients in proportions, for example, as shown below.

Ingredients	Amounts
2-n-Butyl-1-[(4-carboxy-naphth-1-yl)methyl]-6-[N-(cyclohexylaminocarbonyl)-amino]benzimidazole	100 mg
magnesium stearate	10 mg
lactose	100 mg

Example 23

The sucrose calcium sulfate dihydrate and orally active Formula (I) compounds are mixed and granulated with a 10% gelatin solution. The wet granules are screened, dried, mixed with the starch, talc and stearic acid, scr ened and compressed into a tablet.

Ingredients	Amounts
2-ethyl-4-[(4-carboxynaphth-1-yl)methoxy]quinoline	75 mg
calcium sulfate dihydrate	100 mg
sucrose	15 mg
starch	8 mg
talc	4 mg
stearic acid	2 mg

Example 24

2-n-Butyl-1-[(4-carboxynaphth-1-yl)methyl]-6-[N-(cyclohexylaminocarbonyl)amino]benzimidazole, 50 mg, is dispersed in 25 mL of normal saline to prepare an injectable preparation.

Example 25

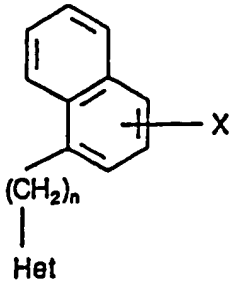
A topical opthamological solution for administering Formula (I) compounds is produced by mixing under sterile conditions the ingredients in proportions, for example, as shown below.

Ingredients	Amounts (mg/mL)
2-ethyl-4-[(4-carboxynaphthyl-1-yl)methoxy]quinoline	1.0
dibasic sodium phosphate	10.4
monobasic sodium phosphate	2.4
chlorobutanol	5.0
hydroxypropanol methylcellulose	5.0
sterile water	q.s.ad 1.0mL
1.0 N sodium hydroxide	q.s.ad pH 7.4

It is to be understood that the invention is not limited to the embodiments illustrated hereabove and the right to the illustrated embodiments and all modifications coming within the scope of the following claims is reserved.

What is claimed is:

1. A compound of the formula:



in which:

X is absent or present as any accessible combination of up to three substituents selected from Cl, Br, F, I, CF_3, C_{1-6}alkyl, NO_2, A-CO_2R^1, tetrazolyl, C_{1-6}alkoxy, OH, SC_{1-6}alkyl, SO_2NHR^1, $NHSO_2R^7$, SO_3H, $CONR^1R^1$, CN, SO_2C_{1-6}alkyl, NR^1R^1, NR^1COH, or NR^1COC_{1-6}alkyl;

each R^1 independently is hydrogen, C_{1-6}alkyl, or $(CH_2)_n$phenyl, wherein the phenyl is unsubstituted or substituted by any accessible combination of up to three substituents selected from Cl, Br, F, I, CF_3, or C_{1-6}alkyl;

A is $-(CH_2)_n-$, $-CH=CH-$, $-Q-CH(R^6)-$, or $-Q-(CH_2)_m-U-(CH_2)_m-$;

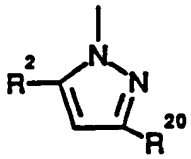
each n independently is 0-4;

each m independently is 1-2;

Q is O, S, NH, NC_{1-6}alkyl;

U is absent or present as O, S, NH, or NC_{1-6}alkyl;

Het is



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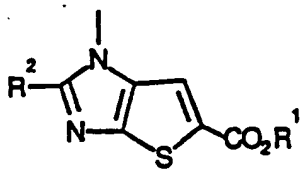

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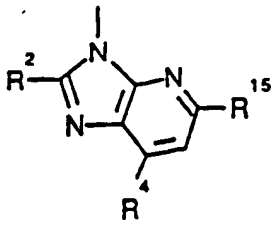

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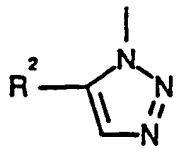

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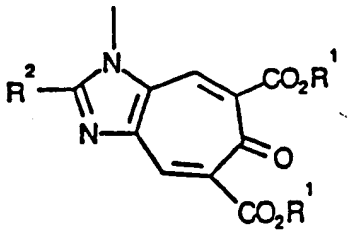

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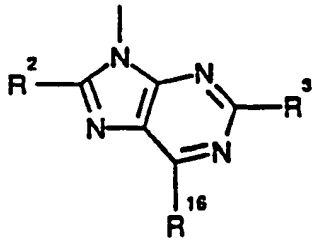

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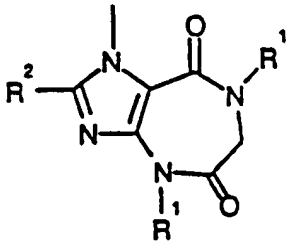

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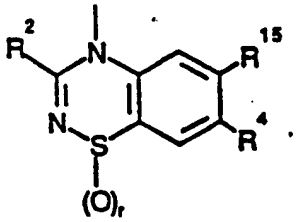

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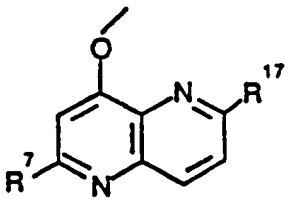

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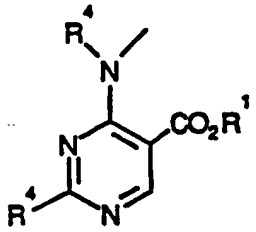

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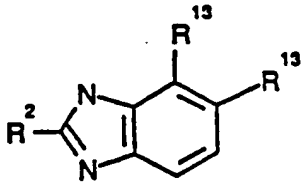

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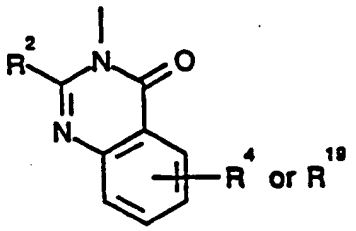

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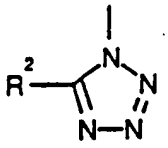

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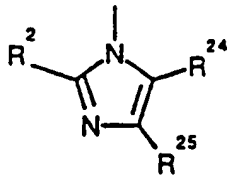

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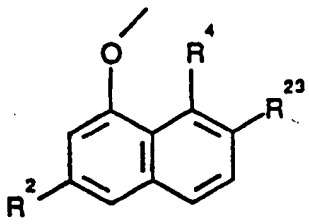

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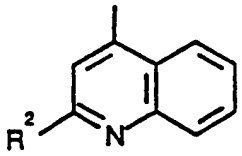

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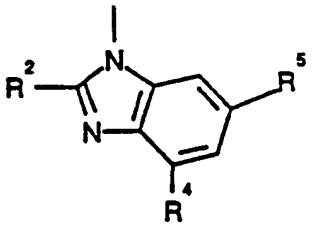

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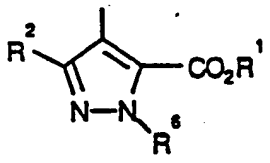

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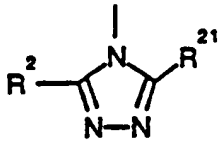

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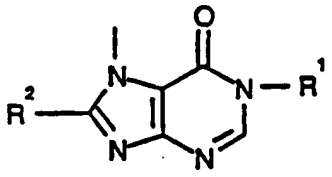

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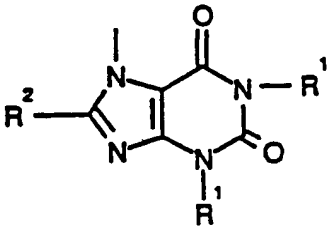

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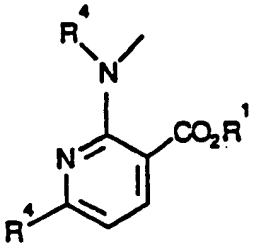

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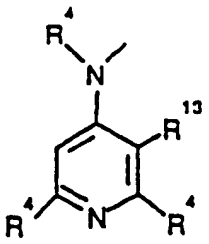

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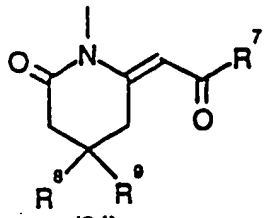

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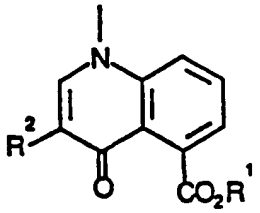

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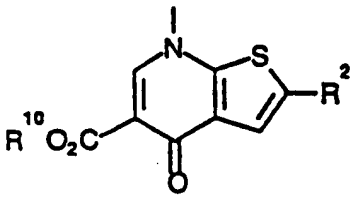
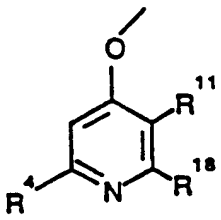
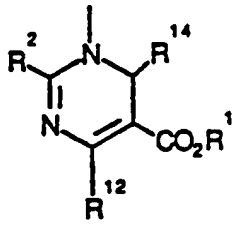


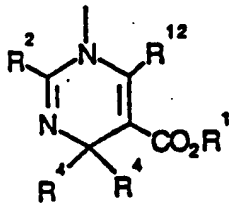
(26)



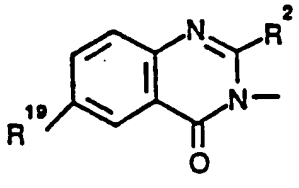
(27)



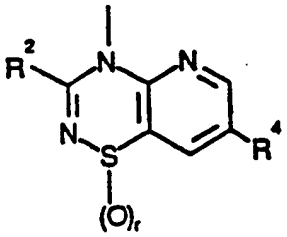
(28)



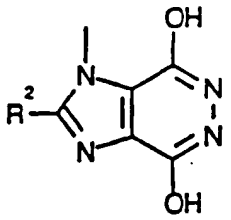
(29)



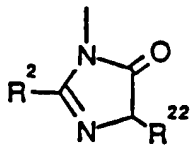
(30)



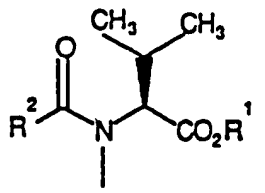
(31)



(32)



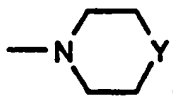
(33)



(34) ;

each R^2 independently is C_{1-8}alkyl, $-OC_{2-8}$alkyl, $-SC_{2-8}$alkyl, $-(CH_2)_{0-2}C_{3-6}$cycloalkyl, $-O(CH_2)_{0-2}$phenyl, or $-S(CH_2)_{0-2}$phenyl, wherein the phenyl is unsubstituted or substituted by any accessible combination of up to three substituents selected from Cl, Br, F, I, CF_3, or C_{1-6}alkyl;

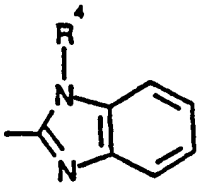
R^3 is Cl, Br, F, I, CF_3, SC_{1-6}alkyl, NR^4R^4, or



;

each R^4 independently is H or C_{1-6}alkyl;

R^5 is



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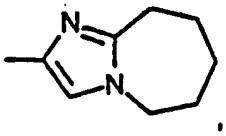

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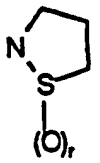

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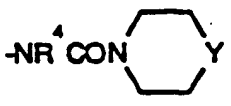
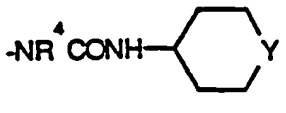


,



, or $-NR^4CONR^4R^4$;

each R^6 independently is H, C_{1-6}alkyl, $-(CH_2)_{1-2}CF^3$, $-(CH_2)_{1-2}C_{3-6}$cycloalkyl, or

$-(CH_2)_{0-2}$phenyl, wherein the phenyl is unsubstituted or substituted by any accessible combination of up to three substituents selected from Cl, Br, F, I, CF_3, or C_{1-6}alkyl;

each R^7 independently is C_{1-4}alkyl or C_{1-4}alkoxy;

R^8 and R^9 independently is C_{1-4}alkyl or R^8 and R^9 taken together are $-(CH_2)_{4-6}-$;

R^{10} is H, C_{1-4}alkyl, or $-(CH_2)_{1-2}OCH_3$;

R^{11} is H, C_{1-4}alkyl, $-(CH_2)_{1-4}-OH$, or CO_2R^1 and R^{18} is R^4 or R^{11} and R^{18} taken together are $-(CH_2)_3-$ or $-(CH_2)_4-$;

each R^{12} independently is H, C_{1-4}alkyl, Cl, Br, F, or I;

each R^{13} independently is CO_2R^1, Cl, Br, F, or I;

R^{14} is C_{1-4}alkyl or =0;

each R^{15} independently is H, C_{1-4}alkyl, or CO_2R^1;

R^{16} is H, C_{1-4}alkyl, Cl, Br, F, I, SC_{1-4}alkyl, or NR^4R^4;

R^{17} is H, C_{1-4}alkoxy, or NR^4R^4;

R^{19} is H, NR^4R^4, or $NR^4C(O)NR^4R^4$;

R^{20} is $-(CH_2)_{1-3}-O-CH_3$, $-(CH_2)_{0-3}-CO_2R^4$ or R_2;

R^{21} is C_{1-6}alkyl, $-(CH_2)_{1-4}OH$, $-(CH_2)_{1-3}-O-CH_3$, $-(CH_2)_{1-2}$-phenyl or $-SCH_2$-phenyl, wherein the phenyl is unsubstituted or substituted by CO_2R^1, Cl, Br, F, or I;

R^{22} is $-(CH_2)_3-$ or $-(CH_2)_4-$;

R^{23} is H, $-O(CH_2)_{1-2}F$, $-OCH_2CF_3$, or $-O(CH_2)_{1-2}NR^4R^4$;

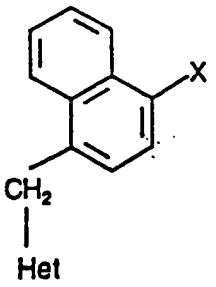
R^{24} is C_{1-4}alkyl, $-(CH_2)_{1-4}-OH$, or CO_2R' and R^{25} is R^4 or R^{24} and R^{25} taken together are $-(CH_2)_3-$ or $-(CH_2)_4-$;

each Y independently is NR^4, O, or CH_2; and

each r independently is 0-2;

or a pharmaceutically acceptable salt thereof.

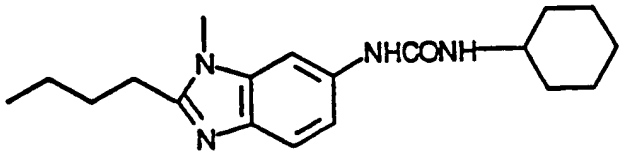
2. The compound according to claim 1 of the formula:



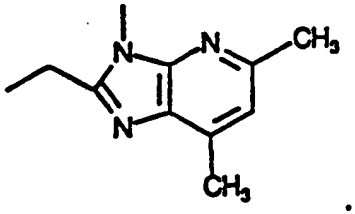
in which X is A-CO_2R^1, $CONR^1R^1$, or tetrazolyl.

3. The compound according to claim 2 wherein X is CO_2H.

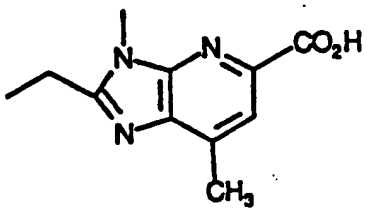
4. The compound according to claim 3 wherein Het is



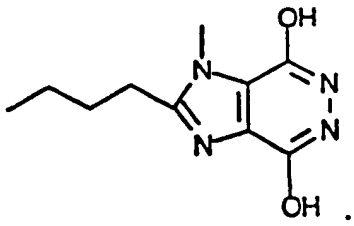
5. The compound according to claim 3 wherein Het is



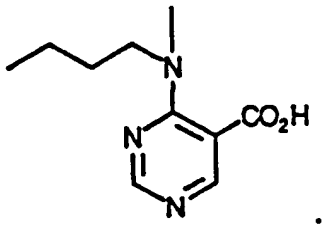
6. The compound according to claim 3 wherein Het is



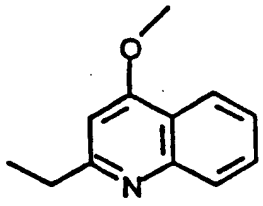
7. The compound according to claim 3 wherein Het is



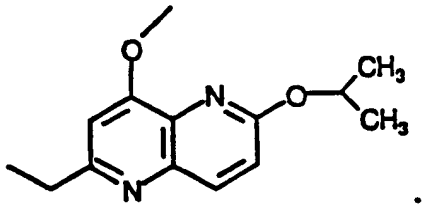
8. The compound according to claim 3 wherein Het is



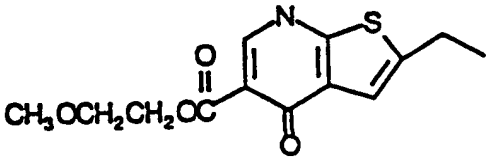
9. The compound according to claim 3 wherein Het is



10. The compound according to claim 3 wherein Het is

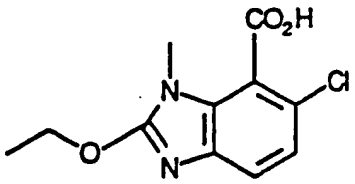


11. The compound according to claim 3 wherein Het is

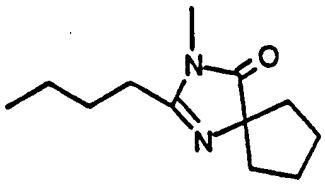


12. The compound according to claim 3 wherein Het

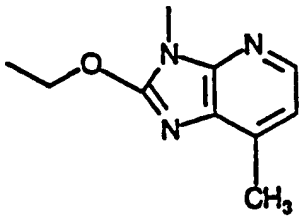
is



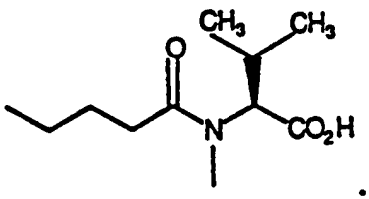
13. The compound according to claim 3 wherein Het is



14. The compound according to claim 3 wherein Het is



15. The comound according to claim 3 wherein Het is



16. A pharmaceutical composition comprising a pharmaceutical carrier and a compound of claim 1.

17. A m thod of antagonizing angiotensin II receptors which comprises administering to a subject in need thereof an effective amount of a compound of claim 1.

18. A method of treating hypertension which comprises administering to a subject in need thereof an effective amount of a compound of claim 1.

19. A method of treating congestive heart failure which comprises administering to a subject in need thereof an effective amount of a compound of claim 1.

20. A method of treating renal failure which comprises administering to a subject in need thereof an effective amount of a compound of claim 1.

21. A method of treating glaucoma which comprises administering to a subject in need thereof an effective amount of a compound of claim 1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/02524

A. CLASSIFICATION OF SUBJECT MATTER
IPC(5) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 540/503; 544/48, 236, 262, 287, 329, 334, 335; 546/114, 118, 122, 152, 153, 156, 290, 301, 304, 310; 548/250, 255, 262.2, 302.7, 303.7, 304.4, 319.1, 335.1, 365.1, 373.1.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE, APS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim N .
Y,P	US, A, 5,276,168 (ATWAL) 04 JANUARY 1994, COLUMNS 1-2, INVENTION SUMMARY.	1-17
Y,E	US, A, 5,312,936 (LIFER ET AL) 17 MAY 1994, COLUMNS 1-3.	1-17
Y	US, A, 5,073,566 (LIFER ET AL) 17 DECEMBER 1993, COLUMNS 1-3.	1-17
Y	US, A, 4,816,463 (BLANKLEY ET AL) 28 MARCH 1989, COLUMNS 1-9.	1-17
Y	US, A, 4,812,462 (BLANKLEY ET AL) 14 MARCH 1989, COLUMNS 1-5 AND CLAIM 1.	1-17
A	US, A, 4,927,822 (BROWN ET AL) 22 MAY 1990.	1-17

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be part of particular relevance
"E" earlier document published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 JUNE 1994	23 JUN 1994
Name and mailing address of the ISA/US	Authorized officer

INTERNATIONAL SEARCH REPORT

International applicati n No.
PCT/US94/02524

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,E	US, A, 5,310,927 (ROSS ET AL) 10 MAY 1994.	1-17
A,P	US, A, 5,245,035 (THOMAS ET AL) 14 SEPTEMBER 1993.	1-17
A,E	US, A, 5,294,631 (FRANZ ET AL) 15 MARCH 1994.	1-17

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/02524

Box I Observations where certain claims were f und unsearchal.le (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

I. Claims 1-17 drawn to a compostion and first method of use.

II. Claim 18, drawn to a second method of use.

III. Claim 19 drawn to a third method of use.

IV. Claims 20 drawn to fourth method of use.

V. Claims 21 drawn to fifth method of use.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-17

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/02524

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (5):

C07D 207/02,18; 209/04, 44; 211/ 36, 56; 213/24, 60, 89; 215/02, 04, 06, 12, 14, 16; 231/10, 12, 14, 54; 233/54, 56, 66 235/02, 04; 237/06, 08, 10, 26; 239/70, 72; 243/10; 249/04, 06, 08, 10; 257/04; 273/00; 285/22; 471/06; 473/02, 26, 40; 487/06; 513/04, 06.

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

540/ 503; 544/48, 236, 262, 287, 329, 334, 335; 546/114, 118, 122, 152, 153, 156, 290, 301, 304, 310; 548/250, 255, 262.2, 302.7, 303.7, 304.4, 319.1, 335.1, 365.1, 373.1.